UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,247	04/01/2004	Varela-Nieto Isabel	1012E-102902US	3032

22798 7590 06/24/2004

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
GRUN, JAMES LESLIE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,247	VARELA-NIETO ET AL.	
	Examiner	Art Unit	
	James L Grun	1641	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/646,468.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/01/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claims 26-48 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809.

It is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated 2F7, 2D1, and 5H6, deposited with the ECACC as accession numbers 98051201, 98031212, and 98030901 are known and publicly available, or can be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the

reproducible production of the cell lines and antibodies necessary to practice the instant invention or filing of evidence of deposit is required. Without a publicly available deposit of the above cell lines, one of skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: the claimed cell line; the cell lines which produce the chemically and functionally distinct antibodies claimed; and/or, the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Therefore, it would require undue experimentation to reproduce the claimed monoclonal antibody species as produced by the hybridomas designated 2F7, 2D1, and 5H6 (ECACC 98051201, 98031212, and 98030901). A suitable deposit of the hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See the criteria set forth in 37 CFR §§ 1.801-1.809.

If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty, that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the biological materials will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

Claims 28, 29, 34-39, and 42-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide description of or enablement for any and every monoclonal antibody population specific for inositol phosphoglycans (IPGs) other than antibodies 2F7, 2D1, and 5H6, produced by the hybridoma cell lines deposited as ECACC accession numbers 98051201, 98031212, and 98030901. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant provides guidance for the above noted monoclonal antibodies and provides no guidance as to what modifications or structure are important for the predictable function of any other monospecific antibody. Very different structures may be found on antibodies with the same specificity as noted above. Conversely, as also noted above, similar structure may be found on antibodies having different specificities. Moreover, the different "types" of IPGs known to the art appear to define groups of IPGs with similar biological activities, but which differ structurally within the group in unknown fashion, and it is not clear what structure of the antigen is required for function in the invention nor would one know based on such as a competitive binding determination if an identical structure or epitope was being bound. In the instant case, the interrelationships of the properties of the three instantly disclosed antibodies are not even clear, so that it is not clear if the antibodies bind to similar members within the structurally diverse populations of IPGs which are grouped on the basis of similar biological activities, or if the different antibodies bind to a similar or cross-reactive epitope, or if 2F7 or 2D1 share the property of lack of cross-reactivity with the variant surface glycoprotein of *Trypanosoma brucei* with 5H6, or if 2F7 or 5H6 function as does

2D1 in the methods for determination of urine IPGs in pre-eclampsia patients. Adequate written description requires more than a mere statement that a molecule is part of the invention and a reference to a potential method of isolating it. Regardless of the complexity or simplicity of the method of isolation of a molecule, the molecule itself is required. Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of molecules by only their functional activity does not provide an adequate written description of the genus. The court indicated that although applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus. For the above reasons, applicant's disclosure of three antibodies of unknown interrelationships and characteristics is found to provide inadequate written description for a genus of related antibodies. Applicant is reminded that the written description provision of 35 USC 112 is severable from its enablement provision. However, in view of the guidance in the instant specification to several antibody species which share unknown and unpredictable structural and functional interrelationships other than sharing the property of apparently binding to members within the two structurally diverse IPG populations, the amount of experimentation required to predictably determine other usable species with unknown functional structures or modifications would also be undue. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (18 USPQ 2d 1027 (CAFC 1991)).

Claims 34-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant exemplifies determination of IPG profiles in serum samples of three patients after glucose ingestion. It is not clear what other samples other than serum/plasma could be used in the invention because applicant provides no guidance to any other samples with predictable changes in IPG levels. One would not know, absent such further description and guidance, what other samples to try in the invention with an assurance of success. One would also not know how to interpret the results of the assay. In this regard, as taught in Shashkin et al. (Diabetologia 40: 557, 1997), a profile similar to that as instantly exemplified for Type I diabetes would be expected in an IPG profile assay from an insulin-resistant Type II diabetes patient. Thus, one would not be able to diagnose/treat a patient at risk of developing Type I diabetes with the method as disclosed and claimed because one would not be able to determine if lack of insulin or insulin resistance was responsible for any lack of changes in the detectable IPG profile after glucose ingestion. Absent further written description and guidance from applicant, one would not be able to practice the invention as claimed.

Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant discloses antibodies which specifically bind to members of both "types" of inositol phosphoglycans (IPGs), without discrimination. Adequate written description requires more than a mere statement that a molecule is part of the invention and a reference to a potential method of isolating it. The molecule itself is required. Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of molecules by only their functional activity does not provide an adequate written description of the genus. The court indicated that although applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus. In the instant application there would appear no descriptive or enabling support for any antibody which **specifically** binds "P-type" inositol phosphoglycans if specificity implies discrimination from "A-type" IPGs.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-33, 35-37, and 39-48 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 27 and claims dependent thereupon, "a hybridoma cell line" should be --the hybridoma cell line-- for proper reference to the previously recited component.

In claim 28 and claims dependent thereupon, "a monoclonal" should be --the monoclonal-- for proper reference to the previously recited component.

In claim 33, "a hybridoma cell line" should be --the hybridoma cell line-- for proper reference to the previously recited component.

Claims 35 and 36 are confusing because the interrelationships of the components and steps to those recited in claim 34 are not clear. For example, it is not clear if a single, or multiple, sample(s) are intended as encompassed.

In claim 37, the in vivo treatment of a patient determined to **have** diabetes does not further limit an in vitro method for determining if a patient is **at risk of developing** diabetes. In this claim it is also not clear what is being determined as the relationship of "determining...risk" as recited in claim 34 to "determined to have or be at risk" is not clear.

In claims 40-41, it is not clear what is encompassed by "soluble IPGs." In claim 41, using is not a valid method step; --with-- is suggested.

In claims 29 and 42, it is not clear what structure(s) is(are) encompassed by "A-type" and/or "P-type" inositol phosphoglycans.

In claim 42, it is not clear what is being determined as the relationship of "determining...has or is at risk of developing" to "determine...is at risk" is not clear.

In claim 44, improper Markush language is used to claim the members of the group. The alternatives "selected from...or" or "selected from the group consisting of...and" are acceptable.

In claim 45, "an antibody" should be --the antibody-- for proper support.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(f) he did not himself invent the subject matter sought to be patented.

Claims 26-33, 39, 40, and 43-48 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Any of Application No. 09/254,745, now U.S. Patent 6,495,330, the filing under 35 U.S.C. § 371 of PCT/GB97/02534 published as WO 98/10791, Application No. 09/254,800, now U.S. Patent 6,716,592, the filing under 35 U.S.C. § 371 of PCT/GB97/02440 published as WO 98/11435, Application No. 09/254,797, now U.S. Patent No. 6,303,580, the filing under 35 U.S.C. § 371 of PCT/GB97/02444 published as WO 98/11116, or U.S. Patent No. 6,271,204, the filing under 35 U.S.C. § 371 of PCT/GB97/02533 published as WO 98/11117 have an inventive entity different from that of the instant application. These references disclose the instantly

claimed monoclonal antibodies, their use in diagnosis and treatment, and methods wherein immobilized antibodies are labelled or are used to capture/isolate IPGs.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 28, 29, 39, and 43-48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Huang et al. (Endocrinol. 132: 652, 1993), in view of Campbell and Maurer et al., and if necessary, further in view of Romero et al. (Proc. Natl. Acad Sci. USA 87: 1476, 1990).

Claims 28, 29, 39, and 43-48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Caro et al. (Biochem. Mol. Med. 61: 214, 1997), in view of Huang et al. (Endocrinol. 132:

652, 1993), Campbell, and Maurer et al., and if necessary, further in view of Romero et al. (Proc. Natl. Acad Sci. USA 87: 1476, 1990).

Either of Huang et al. or Caro et al. teach the isolation of inositol phosphoglycan insulin mediators. Huang et al. teach the use of polyclonal antibodies which bind to the mediators in assays inhibiting the biological activities of the mediators (see e.g. page 654). The references do not teach monoclonal antibodies specific for the mediators.

Campbell teaches (page 29) that affinity purification uses of monoclonal antibodies are known to the art and that "[i]t is customary now for any group working on a macromolecule to...make monoclonal antibodies to it (sometimes without a clear objective for their application)."

Maurer et al. teach that the method by which an immunogen is presented to a host can influence the ability of that immunogen preparation to elicit a response, e.g. by employing the correct "carrier" and conjugation procedure, an immune response to almost any macromolecule (even those believed to be nonimmunogenic) can be elicited (page 50). Further, the reference teaches typical methods for the production of both polyclonal and monoclonal antibodies (pages 64-67).

Romero et al. teach the use of anti-IPG antibodies in an ELISA assay.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited monoclonal antibodies to the inositol phosphoglycan insulin mediators of either of Huang et al. or Caro et al. because either of Huang et al. or Caro et al.

teach that the mediators are of unquestioned research and clinical interest and Campbell teaches that it is customary to do so. It would have been obvious to have generated monoclonal antibodies in order to provide a potentially unlimited source of homogeneous reagent for uses such as affinity purification, functional studies, or clinical studies of the macromolecules. One would have had an extremely reasonable expectation of success as Huang et al. teach that the structures of the mediators are antigenic and bind antibodies elicited to a structurally similar macromolecule and Maurer et al. teach that an immune response can be elicited to almost any macromolecule. If necessary, Romero et al. provide further motivation for the labelling and solid-phase immobilization of anti-IPG antibodies as taught by Caro et al., as modified in view of Huang et al., Campbell, and Maurer et al. in view of the disclosed use of anti-IPG antibodies in an ELISA assay. The examiner would note that one does not require a monoclonal antibody to an epitope in order to have previously elicited antibodies to that epitope or to elicit further antibodies to that epitope.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

The Examiner takes Official notice that treatment of a patient determined to have type I diabetes with insulin is notoriously old and well known in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone numbers for official facsimile transmitted communications to TC 1600, Group 1640, are (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

JLG

James L. Grun, Ph.D.
June 21, 2004

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641